Restriction Requirement

In a telephone call to applicants' representatives, the Examiner required restriction under 35 U.S.C. § 121 between Group I, Claims 14-17 and 24 drawn to a non-human mammal; Group II, Claims 18-23 drawn to a non-human mammal cell; Group III, Claim 25 drawn to a method of screening medicaments using a non-human mammal according to claim 1; Group IV, Claim 25, drawn to a method of screening medicaments using a non-human mammal cell according to claim 18 or 19; and Group V, Claim 26 drawn to a medicament. During a telephone conversation on October 8, 2002, a provisional election without traverse was made to prosecute the invention of Group I, claims 14-17 and 24. Applicants hereby affirm the election of the invention of Group I, claims 14-17 and 24, without traverse.

Applicants have cancelled claims 18-23, 25, and 26 for the sole reason that these claims were not elected in response to a restriction requirement and, therefore, were withdrawn from consideration. Accordingly, applicants reserve the right to prosecute claims directed to the inventions of claims 18-23, 25, and 26 in one or more divisional applications. Applicants also reserve the right to request rejoinder of the subject matter of claim 25 should any claims corresponding to the subject matter of Group I be allowed.

Objections to the Specification

The Office objected to the specification, asserting in particular that (1) the Brief Description of the Drawings was not properly placed; and (2) the specification does not comply with 37 C.F.R. § 1.77(b), which does not allow for sections titled "Problems to be Solved by the Invention" or "Means for Solving the Problems". Applicants have

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amended the specification, as requested by the Office, for the sole purpose of facilitating prosecution. Accordingly, applicants respectfully request that the requirement that the specification be amended be withdrawn. Applicants note that the new headings, just as the old, do not impart meaning to the various parts of the specification, but rather serve to convenience the reader.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 14-17 and 24 were rejected under 35 U.S.C. § 112, first paragraph, for a number of reasons that, taken together, led the Office to conclude that the specification "does not reasonably provide enablement for any non-human mammal modified to inhibit the expression of its α-tocopherol protein transfer gene produced by using any cell harboring a disruption in the α-tocopherol protein transfer gene as broadly claimed." (Paper No. 8 at 6.) Applicants respectfully traverse. As set forth below, the cited references do not support the assertion of lack of enablement.

First, the Office contends that "[t]he state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics." (*Id.* at 6.) In support of this assertion the Office relies on three art references—Leonard (1995), Moens (1993), and Griffiths (1998).

The Office characterizes Leonard (1995) as disclosing "mice with a disruption in the g_c gene which were intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits." (*Id.* at 6.) The Office notes that one of these allegedly unexpected traits is that the "knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally." (*Id.* at 6.) The

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Office characterizes Moens (1993) as "[teaching] two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null ...." (*Id.* at 6.) Finally, the Office characterizes Griffiths as "teach[ing] that despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes...." (*Id.* at 6-7.) The Office then asserts that these alleged teachings of the cited references support the proposition that the phenotype of knockout mice was unpredictable. (*Id.* at 7.) Applicants respectfully traverse.

First, with respect to the Leonard reference, the Office's characterization of the experimental results contradicts that of the authors themselves, who characterize the knockout mice disclosed as "exhibit[ing] a wide range of interesting immunological abnormalities, some shared by humans with XSCID and some that are different." Based on their assessment of the knockout mice, the authors concluded that "the mutant γ_c mice provide a valuable animal model of γ_c deficiency." (Leonard, abstract.) Accordingly, the phenotype of the mutant mice, while perhaps not an exact replica of the phenotype of humans with XSCID, is similar enough that the authors of the reference consider the knockout mice to represent a successful experiment; that is, in making the mice the investigators have succeeded in creating an animal model for XSCID. Thus, Leonard does not support the allegation of unpredictability of mouse phenotypes. Indeed, Leonard provides evidence of predictability, not unpredictability, with respect to generating animal models of human diseases by use of knockout technology.

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With respect to Moens, the reference itself notes that the N-myc gene is involved in many processes and that various mutant forms of the gene lead to various mutant phenotypes. (Moens, abstract and first two paragraphs of introduction.) The authors generated two mutant alleles of N-myc and found that one mutant allele was a hypomorph (the allele produced a protein which was partially functional) and a second mutant allele was a null allele (the allele did not produce any functional protein). Entirely consistent with the diverse functions of N-myc, the authors observed that mouse embryos homozygous for either mutant allele and mouse embryos compound heterozygous for the two alleles (that is, embryos containing one copy of each mutant allele) display unique phenotypes that are dependent upon their genotype.

Thus, these three different phenotypes simply represent that the authors conducted three different experiments, each experiment asking what the phenotype of a particular distinct genotype would be. Nothing in the reference suggests that any of the three different phenotypes observed was itself unpredictable.

With respect to Griffiths, applicants note that the passage cited by the Office compares the phenotype of spontaneous rat mutants in the gene and knockout mouse mutants generated using homologous recombination. This does not speak to whether the approach of generating knockout mutants as a means of generating models of human diseases predictably yields the sought-after model.

To the extent the reference does relate to predictability, Griffiths notes that in both mouse mutants and in diseased (mutant) humans, "there is no clear understanding of how the nature and position of [a] mutation [in the PLP gene] correlates with the phenotype [observed in the mutant mouse or the human patient suffering from PMD or

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SPG.]" (Griffiths at page 347, col. 2, first full paragraph.) That the animal model is no more predictable than the human disease it is designed to model is not evidence of unpredictability in the process by which the model was made; rather, it is evidence that the model is indeed mimicking the human disease with a high degree of fidelity.

Applicants submit that, for all of the reasons described above, Leonard (1995), Moens (1993), and Griffiths (1998) do not demonstrate that the state of the art at the time of filing was that one could not predict the phenotype of transgenic non-human mammals generally.

In any event, applicants note that mice are the only non-human mammals encompassed by new claims 27-34. Applicants' disclosure makes clear that mutant mice, as claimed, comprising "a knockout allele of the genomic α-TTP gene, wherein expression of α-TTP from the knockout allele is inhibited, such that transgenic mice homozygous for the knockout allele exhibit a vitamin E deficiency phenotype" as in, *e.g.*, claim 27, are enabled by applicants' disclosure.

By these amendments, applicants do not acquiesce in the Office's argument that the specification only enables mice. Instead, this amendment is made only to facilitate prosecution without disclaimer or prejudice to a future prosecution of the cancelled subject matter.

The Office next asserts that "species-specific requirements for transgene design are not clearly understood" and contends that "[e]xamples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes." (Paper No. 8 at 7.) The "examples" of "widely varying phenotypes" to which the Office alludes are two instances that the Office

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characterizes as models of human diseases that "have relied on transgenic rats when the development of mouse models was not feasible." (*Id.* at 7.) Specifically, Mullins (1990) and Hammer (1990) are described by the Office as describing transgenic rats expressing a mouse *Ren-2* transgene and a human HLA-B27 allele, respectively. (*Id.* at 7.) According to the Office "[b]oth investigations [in rats] were preceded by a failure to develop human-like symptoms in transgenic mice ... expressing the same transgenes that successfully caused the desired symptoms in transgenic rats." (*Id.* at 7, references omitted.)

Applicants note that Mullins (1990) and Hammer (1990) describe transgenic rats that are structurally distinct from the transgenic non-human mammals of applicants' claims. Applicants' claims encompass transgenic non-human mammals, and methods of making transgenic non-human mammals, where the non-human mammals comprise a knockout allele of the genomic α-TTP gene. As described in applicants' specification and as well known in the art, a knockout allele is generated through the process of homologous recombination is cultured cells, such as embryonic stem cells. (*See* Application at page 5, line 22 – page 7, line 12.) In contrast, Mullins (1990) and Hammer (1990) describe transgenic rats that are made by the distinct process of pronuclear injection of fertilized eggs. (Mullins, legend to Fig. 1; Hammer at page 1110, col. 2.) The pronuclear injection technique does not create a knockout allele; rather, the injected DNA construct randomly integrates into the genome. (*See* Overbeek (1994), cited by the Office in Paper No. 8.)

As partially described in Overbeek (1994), the random integration of the DNA construct following pronuclear injection means that the integrated DNA is largely at the

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mercy of the adjacent DNA at the cite of integration. The construct may integrate at a location of the genome that does not allow for its expression or that modulates its expression, either increasing or decreasing the level of expression or giving rise to ectopic expression. A second consequence of random integration of the construct is that the gene being expressed using pronuclear injection must be linked to a promoter and enhancer sequences that are included in the construct. In essence, the gene must carry these sequences along with it so that they will integrate into the genome together with it and regulate its expression after integration.

Because of all of these well known characteristics of pronuclear injection transgenics, the Office concluded that "the combination of elements (protein, promoter, species of protein, and species of transgenic) required obtain a desired effect were not within the realm of routine experimentation at the time of filing." (Paper No. 8 at 7.) Applicants do not necessarily agree with the Office's conclusion but, regardless, this issue is inapposite to the question of whether applicants' pending claims are enabled.

Applicants' pending claims encompass transgenic mice comprising a knockout allele of the genomic α-TTP gene. These claims further require that expression of α-TTP from the knockout allele is inhibited, such that transgenic mice homozygous for the knockout allele exhibit a vitamin E deficiency phenotype. As described in applicants' specification, this inhibition of expression in a knockout allele can be caused by either a disruption of part of the α-TTP gene or disruption of a regulatory region of the α-TTP gene. (Application at page 5, lines 23-26.) None of the factors cited by the Office relating to potential points of difficulty in practicing pronuclear injection transgenesis are relevant to practicing these claims. Applicants are not expressing a protein that is not

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normally expressed; instead, applicants are inhibiting gene expression, by making a knockout allele of a gene. Pronuclear injection transgenesis is not relevant to enablement of making a knockout allele.

The same arguments apply to the Office's reliance on the discussion in Wall (1996) and Overbeek (1994). Both references relate to pronuclear injection, and the Office has failed to establish how any alleged uncertainty in the making of pronuclear injection transgenics is relevant to whether making knockouts is enabled. Without such a link, these references are irrelevant to the enablement of the pending claims.

The Office next alleges that "[t]he art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse." (Paper No. 8 at page 8.) As noted above, without acquiescing in any way to the Office's position, new claims 27-34 recite "A transgenic mouse ...." Applicants submit that this language renders this rejection moot. Accordingly, applicants respectfully submit that this basis of rejection should be withdrawn.

Finally, the Office contends that the specification does not "enable making and/or using a transgenic having a phenotype other than vitamin E deficiency as broadly encompassed by the claims." (*Id.* at 9.) Again, without acquiescing in any way to the Office's position, applicants note that the rejected claims have been cancelled and that the vitamin E deficiency phenotype is recited in new claims 27-34, thus obviating the basis for this rejection. Accordingly, applicants respectfully submit that this rejection should be withdrawn.

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Rejections Under 35 U.S.C. § 112, second paragraph

Claims 14-17 and 24 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. (Paper No. 8 at 10.) Specifically, the Office objected to the use of the terms "artificial" and "modified" and to the phrase "animal belonging to Rodent". Applicants note that the rejected claims have been cancelled. The new claims do not include the terms "artificial" or "modified", nor the phrase that the Office objected to. Accordingly, the rejections under 35 U.S.C. § 112, second paragraph are moot in view of the amendments to the claims and this rejection can be withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims 27-34.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: April 18, 2003

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